

## Cutaneous Necrosis Complicating the Injection of Pegylated Interferon $\alpha$ -2b in a Patient with Chronic Hepatitis C

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**SUMMARY** Pegylated interferon  $\alpha$  (PEG-IFN- $\alpha$ ) is a formulation of recombinant human interferon conjugated with polyethylene-glycol. This preparation has a long half-life (compared with conventional IFN), which allows for once-weekly injection. Elimination half-life of PEG-IFN- $\alpha$  2b is 22-60 hours (average, 35-40 hours). We report the development of a local necrotizing reaction complicating subcutaneous injection of PEG-IFN in a patient with hepatitis C. This case enhances the need of careful training in drug reconstitution and self injection, with as much variation as possible of the injection site.

**KEY WORDS:** hepatitis C, interferon alfa, ribavirin, side effects, cutaneous necrosis

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### INTRODUCTION

Type 1 interferons (IFN) are a group of proteins with antiviral, antiproliferative and immunoregulatory actions. IFN- $\alpha$  is currently employed in the treatment of viral hepatitis, Kaposi's sarcoma, malignant melanoma, renal cell carcinoma, hairy cell leukemia and chronic myelogenous leukemia. A greater efficacy in the treatment of chronic hepatitis C has been recently achieved with once-weekly dosing of PEG-IFN- $\alpha$  in combination with ribavirin, which is now the standard therapeutic protocol for hepatitis C (1). PEG-IFN- $\alpha$  has a molecular weight of approximately 12 kD, is reabsorbed more slowly and therefore remains in the circulation longer than conventional IFN- $\alpha$ . This therapeutic combination may be responsible for systemic and cutaneous

side effects. Local reactions at the sites of IFN injection may be the cause of significant concern. A common side effect at injection site is localized inflammatory skin lesion, which may occasionally progress to skin necrosis with ulceration (2-6).

### CASE REPORT

A 48-year-old Caucasian male was receiving once-weekly subcutaneous injection of PEG-IFN- $\alpha$  2b (100  $\mu$ g) and oral ribavirin (1000 mg per day) for chronic active hepatitis C (HCV-RNA genotype 1b, Ishak stage=2). After 6 months of therapy, the patient noted the appearance of an indurated and erythematous plaque on the right shoulder, three cm below the usual area of injection. The patient

continued to inject himself at the same site, alternating with the left shoulder. Several weeks later, a black eschar developed in the center of the plaque and enlarged progressively. A similar papular lesion of 0.5 mm in diameter appeared on the left shoulder. When the patient presented for examination, there was a painful reddish 3x1.5 cm plaque on the right shoulder, at the deltoid muscle insertion in the humerus. The plaque was indurated and poorly delimited with a central necrotic area. Removal of the black eschar revealed a deep ulcer with fibrinous content (Fig. 1). A small erythematous papule was present on the left shoulder. Cultures for bacterial and fungal agents were negative. Skin biopsy taken from the inflammatory margin of the ulcerated lesion showed superficial erosion of the epidermis with necrotic keratinocytes, and dermal necrosis extending to the subcutaneous fat. Mononuclear cells, neutrophils and eosinophils were present within the superficial and deep dermis in perivascular, periadnexal and interstitial locations. Focal red blood cell extravasation was also noted, but no signs of vasculitis were present. At the moment of our observation, laboratory studies including ESR, CRP, liver enzymes and complement fraction were within the normal range. Cryoglobulins and HCV-RNA level were undetectable. The lesion was treated with antiseptics and topical corticosteroids and resolved slowly over 2 months. The lesion on the left shoulder was treated with topical corticosteroids with complete resolution in two weeks. PEG-IFN- $\alpha$  2b continued to be injected subcutaneously into the thigh, without interruption or dose modification



**Figure 1.** Necrotic ulcer occurred 3 cm below the site of pegylated interferon injections.

for another four months. No new cutaneous lesions developed either at the injection site or elsewhere.

## DISCUSSION

The most common side effects of PEG-IFN- $\alpha$  are similar to those of IFN- $\alpha$ , including mild, reversible bone marrow suppression and flu-like symptoms (7). Injection site reactions are considered as mild to moderate in severity, and most consist of local inflammatory reactions. They occur at approximately twice the incidence with PEG-IFN- $\alpha$  treatment compared to IFN- $\alpha$ , possibly due to longer serum half-life of PEG-IFN resulting in greater tissue permeation. Mild inflammation without serious or persistent reaction has been noted in approximately 40%-45% of patients (8), and is more common during the first injections (4). In the literature there have been case reports of sarcoidosis and eczematous reaction patterns of adverse dermatologic effects during PEG-IFN- $\alpha$  treatment for chronic hepatitis C (9-11). Cutaneous necroses are unusual and occur without age or sex predominance, and regardless of whether the IFN injection is given subcutaneously or intramuscularly. Although reported to arise most frequently on the abdominal wall and the anterior surface of the thighs, they can also be seen overlying the deltoid or triceps. Necrotic reactions are usually delayed, as they most often occur 2-3 months of the start of treatment, but can be observed from few weeks to years after therapy initiation. They are not correlated to the dose or frequency of administration. Erythematous and often painful patches or indurated nodules become violaceous and then necrotic with a minimally purulent base. The necrosis spreads progressively and forms a dry, black escharotic plaque with irregular borders, often angular and well defined. The size of the ulceration varies from several millimeters to 10 cm in diameter. The edge of the ulceration is comprised of a large inflammatory plaque, infiltrated on palpation and poorly delimited. The lesions can be multiple. Resolution under treatment is slow, taking weeks to months, leaving hyperpigmented and atrophic scars (12). Although the exact mechanism involved in the pathogenesis of cutaneous necrosis remains unknown, several observations support different pathogenic mechanisms: hypercoagulability, local vasospastic effect, intra-arteriolar injection and immune-mediated mechanisms (8,12-14). Our observation emphasizes the occurrence of cutaneous necrosis following injection of the pegylated form of IFN- $\alpha$  (2,6,8,15). Usually the

skin lesion develops at the injection site, but in our patient the reaction occurred three cm below the site of injection, at deltoid muscle insertion in the humerus. We postulate a physical concentration of IFN in this area.

It has been suggested that injections site reactions including skin necrosis are more likely if the IFN powder is not reconstituted with the appropriate volume of diluent, resulting in an inappropriately high concentration of the drug (13). This explains the intermittent nature of these reactions in patients who prepare the injection by themselves. Rotation of injection sites has been recommended to decrease the additive inflammatory effects of repeated injections in the same site (14,15). Medical treatment is mostly based on the application of hydrocolloid bandages to hasten healing, associated with local and systemic antibiotics in the rare cases of superinfection. It is sometimes necessary to resort to surgical debridement and excision of the lesion, followed by direct suturing or grafting. Continuation of IFN injection at distant sites is possible for most patients, but can be complicated by the appearance of new cutaneous necroses at the new injection sites, which may necessitate discontinuation of the drug. Prevention requires competent training in self injection, with as much rotation as possible of the injection site, and particular vigilance in cases of erythema showing persistence for several days at the injection site (14). Because PEG-IFN has almost completely replaced IFN for its most frequent indications, continuous awareness of the possibility of cutaneous necrosis is relevant to early diagnosis and to change injection site.

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